Summary

The inability to talk does not diminish an animal's ability to experience pain, though it may hinder the recognition and therefore lead to the under-treatment of pain. Pain assessment and treatment in horses has advanced considerably recently with the publication of numerous research papers in this area. This review will summarise recent research findings and suggest how advances in knowledge of peri-operative pain management can be implemented in equine clinical practice.

Introduction

Unresolved stress or pain behaviour was recently identified as one of the four priority welfare challenges facing horses in the UK (Horseman, 2017). It is imperative that equine clinicians both assess pain in horses presented for veterinary attention and ensure that pain management protocols are optimised as far as possible for individual horses.

The understanding of the physiology of pain has evolved from the concept of a simple reflex arc to one that involves many complex interactions at all levels of the peripheral and central nervous system (Livingston and Chambers, 2000). Acute pain usually results from a specific injury or disease and has a biologic function whereas chronic pain can be considered as a disease entity in itself (Lamont et al., 2000). In chronic pain synaptic plasticity of the central nervous system results in increased transmission of pain and a reduction in pain thresholds at the site of original injury and also areas distant to it (Ji et al., 2003). The difference pain and nociception is relevant when evaluating results of clinical and experimental studies investigating analgesics. Pain is defined by the International Association for the Study of Pain (IASP) as *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* (https://www.iasp-

pain.org/Taxonomy). Measuring pain in animals is challenging so studies often measure nociceptive responses using electrical, mechanical or thermal stimuli (Moens et al., 2003) Nociceptive threshold testing is a useful technique but does not replicate the complete pain experience that is seen in clinical cases and this disparity can lead to differences in response to a drug in an animal presenting with clinical pain compared to an experimental model.

The treatment of pain is dependent upon the recognition of pain. Horses in pain may show "*'low' and/or 'asymmetrical' ears, an angled appearance of the eyes, a withdrawn and/or tense stare, mediolaterally dilated nostrils and tension of the lips, chin and certain facial muscles*" (Gleerup et al., 2015) along with changes in behaviour (Price et al., 2003). Generalised behavioural changes occur regardless of the type of pain stimulus, but these are often accompanied by more specific localising pain behaviours or physiological changes (Gleerup and Lindegaard, 2016). An increase in composite pain scale (CPS) and horse grimace scale (HGS) has been seen in ponies following castration (Dalla Costa et al., 2014), with similar results following arthroscopic surgery (Price et al., 2003). An association between CPS score and survival without complication has been found in horses after emergency gastrointestinal surgery (van Loon et al., 2014).

A review on the recognition and quantification of pain in horses along with a practical guide to the implementation of pain assessment protocols in horses was recently published in this journal and should be consulted for an in depth discussion of this topic (Gleerup and Lindegaard, 2016).

The finding that surgery is painful is unsurprising, yet in 2005 only 36.9% of UK equine vets provided analgesia following castration (Price et al., 2005). Hopefully, with increasing awareness of equine pain behaviours and more data regarding the use of analgesics in horses this under-treatment will have improved. The reluctance to use analgesics is not limited to the

UK. In New Zealand 55% of veterinarians have morphine available for the treatment of horses, but 13% only use it (Waran et al., 2010). In an international survey of veterinarians who perform equine anaesthesia 81.2% of respondents used methadone and 77% morphine "rarely" or "not at all" (Wohlfender et al., 2015). The tendency towards older analgesics is also highlighted with 69% of equine vets using Phenylbutazone or Flunixin either "as standard" or "frequently" (Wohlfender et al., 2015), with 95% of UK equine veterinary surgeons prescribing Phenylbutazone or Flunixin. This is in contrast to small animal practice where there is a move towards more recently licenced treatments (Hunt et al., 2015).

An effective perioperative analgesic plan starts before the procedure and should be appropriate to the diagnosis, planned surgery and duration of expected postoperative discomfort. Pre-emptive analgesia will result in clinically effective drug concentrations before surgery begins. An understanding of drug pharmacology and pain pathways is essential and assists with the formulation of an individualized multimodal drug protocol which targets the pain pathways at multiple levels (Muir, 2010). The theory behind the use of a multi-modal technique is that lower doses of individual drugs can be used by taking advantage of additive and synergistic effects that certain drugs show when given together with a consequent reduction in side effects (Lamont, 2008).

Locoregional anaesthesia plays an important role in equine pain management protocols and should be used with systemic analgesia whenever possible.

The horse is classified as a food producing animal within the EU, and therefore medicines mentioned in this article should be prescribed in accordance with BEVA guidelines (www.beva.org.uk). Medicines prescribed for competition horses should be checked against the Equine Prohibited Substance List (https://inside.fei.org/fei/cleansport/ad-h/prohibited-list). Commonly used analgesic drug doses are listed in Table 1.

Systemic Analgesics

Alpha-2 adrenoceptor agonists

Alpha-2 adrenoceptor agonists produce sedation by acting on the locus coeruleus in the brainand analgesic effects via actions on supra- and spinal tissues (Murrell and Hellebrekers, 2005). The antinociceptive properties of the alpha-2 adrenoceptor agonists have been demonstrated using both visceral and mechanical pain models (Moens et al., 2003, Muir and Robertson, 1985). However, in clinical cases their sedative effects can confound the interpretation of their analgesic effects, particularly as the sedative effects outlast the analgesic properties (Chambers et al., 1993). Increased alpha-2 adrenoceptor selectivity should theoretically lead to increased analgesic efficacy, especially as alpha-1 adrenoceptor agonist activity has been found to interfere with alpha-2 adrenoceptor mediated analgesia (Gil et al., 2009). The alpha-1:alpha-2 selectivity is 1:160 for xylazine, 1:260 for detomidine, 1:360 for romifidine and 1:1620 for (dex-) medetomidine (Sinclair, 2003, Scheinin et al., 1989). Other mechanisms of analgesia may play a role as the in vivo analgesia does not precisely follow the increasing alpha-2 adrenoceptor selectivity, with detomidine providing better analgesia than romifidine against electrical stimulation of cutaneous regions (Moens et al., 2003). This finding may not translate precisely to clinical manifestation of pain (Hamm et al., 1995, Moens et al., 2003).

Constant rate infusions of alpha-2 adrenoceptor agonists are commonly used for sedation in standing horses and to supplement inhalant anaesthetic techniques (partial intravenous anaesthesia). Following an initial loading dose the aim is to administer the drug by infusion to achieve stable plasma drug concentrations. This should avoid peaks and troughs in analgesia or sedation and potentially lead to fewer side effects. The pharmacokinetic profile of (dex-) medetomidine makes it a good choice for intraoperative continuous rate infusion

(CRI) (Bettschart-Wolfensberger et al., 1999)., A significant reduction in isoflurane requirement is seen with medetomidine CRI (K Neges et al., 2003), and dexmedetomidine is associated with improved recovery scores with only limited cardiopulmonary effects (Marcilla et al., 2012). The use of a CRI of an alpha-2 adrenoceptor agonist results in a subjectively more stable plane of anaesthesia and less requirement for additional anaesthetic top-ups (K Neges et al., 2003) although it is not clear whether this is a result of their antinociceptive effects or as a consequence of MAC reduction. Dexmedetomidine or medetomidine do not have a Marketing Authorisation for administration to horses making their routine use difficult to justify. Romifidine and detomidine are licensed alternatives and also have an isoflurane-sparing effect (del Barrio 2017).

Although the alpha-2 adrenoceptor agonists lead to a reduction in intestinal motility the precise effect of an intraoperative CRI on postoperative gastrointestinal function is not clear and their effects on postoperative analgesia requirements have not yet been established. Their use may contribute to a multimodal protocol but they should not be relied upon as the sole analgesic.

Ketamine

Ketamine is a phencyclidine derivative and is the most commonly used agent for the induction of general anaesthesia horses (Wohlfender et al., 2015). Sub-anaesthetic doses produce analgesia by interacting with NMDA receptors. In chronic pain states NMDA receptor antagonism limits the development of central sensitisation by inhibiting temporal summation and secondary mechanical hyperalgesia (Woolf, 2011). Ketamine is commonly presented as a racemic mixture of the R(-) and S(+) enantiomers though enantiopure preparations containing the S(+) isomer are available. S(+)-Ketamine is twice as potent as the racemic mixture and is associated with faster recovery times. These possible benefits have led

to preliminary investigations into its use in the horse (Canola et al., 2015, Casoni et al., 2015, Larenza et al., 2009) though this preparation does not have a veterinary Marketing Authorisation.

In healthy patients, after administration of ketamine direct stimulation of the central nervous system leads to increased sympathetic tone and subsequent increases in blood pressure and heart rate. In sick patients the direct depressant effects of ketamine on the myocardium may become apparent due to depletion of catecholamine stores within the sympathetic system. A MAC sparing effect of 37% was found under halothane anaesthesia when ketamine was given by CRI whilst increasing cardiac output (Muir and Sams, 1992). Low dose ketamine infusion (20 mcg/kg/min) in conscious experimental horses reduces the response to electrical cutaneous stimulation (Peterbauer et al., 2008). The same can be found in clinical cases; horses with naturally occurring laminitis that received 0.6mg/kg/hr ketamine for six hours once daily for three days, alongside tramadol twice daily, had increased forelimb loading both during and after treatment and this was attributed to ketamine's effect on central sensitization (Guedes et al., 2012). The same laminitic horses also had lower concentrations of circulating inflammatory prostaglandins TNF-α and thromboxane B(2) indicating an anti-inflammatory effect of systemic ketamine use. Clinical experience suggests that a low dose ketamine CRI may have some benefit in cases that involve orthopaedic and integument pain that is not responding to conventional treatment with opioids and NSAIDs, though it may be of less use in visceral pain (Matthews et al., 2004).

Opioids

Opioids, particularly butorphanol, are often included in sedation protocols though perioperative use of opioids is still limited in equine practice (Wohlfender et al., 2015). This may be related to apprehension over possible side effects, with the potential for excitability

following intravenous injection and decreased intestinal motility following general anaesthesia being commonly stated concerns (Clutton, 2010).

Horses that received a morphine bolus followed by a CRI during halothane anaesthesia had similar haemodynamic variables to those that did not (Clark et al., 2005)and the administration of morphine was also associated with the need for less additional anaesthetic agent, fewer attempts to stand and shorter times to standing (Clark et al., 2005, Clark et al., 2008, Love et al., 2006). The optimal dose of morphine for analgesia in clinical cases has not yet been established. The early dose-response studies investigated relatively high doses of morphine in small numbers of pain-free, healthy horses using experimental threshold testing assays rather than clinical pain (Kalpravidh et al., 1984b, Roger et al., 1985).(Kalpravidh et al., 1984b). In horses undergoing airway surgery 0.2 mg/kg bwt had no additional benefits over 0.1 mg/kg bwt on the duration or quality of recovery following anaesthesia although the surgery performed was relatively non-invasive (compared to orthopaedic surgery) and post-operative pain was not assessed (Love et al., 2006). Conflicting results on the association of post anaesthetic colic and the use of morphine may lead to difficulties when deciding on its use. In one retrospective study the use of morphine was associated with a four-fold increase in the risk of colic following orthopaedic surgery (Senior et al., 2004), however another retrospective study found no increased incidence of post anaesthetic colic in horses that received morphine compared to those that did not (Andersen et al., 2006). Morphine is associated with an increase in locomotor activity in healthy pain free horses (Carregaro et al., 2007). This increase in locomotor activity is less likely to be seen in horses having surgery or those that are already experiencing pain (Mircica et al., 2003, Muir, 1981), with horses that received 0.1 mg/kg bwt morphine for sedation for standing surgery showing no intraoperative ataxia or locomotor activity (Potter et al., 2016). The conflicting arguments presented above highlight the different findings that may be seen in experimental and clinical studies and

explain why the use of systemic morphine in horses is controversial. More data is available to support the use of morphine by the epidural or intraarticular routes in horses.

Buprenorphine has a marketing authorisation in the UK for postoperative analgesia in horses. It produces antinociception to thermal stimuli (Love et al 2012) and these experimental findings were provided more effective postoperative analgesia than butorphanol after elective surgical procedures performed under general anaesthesia without detrimental effects (Taylor et al., 2016, , . The use of buprenorphine in combination with Detomidine via CRI for standing surgery resulted in more complications than the use of morphine (Potter et al., 2016). All horses that received buprenorphine showed box walking and tremors/shivering, half of the horses were hypersensitive to noise in the postoperative period. No horses that received morphine showed complications, though only a small sample size of four horses per group was used. This increased incidence of side effects in the buprenorphine group may be due to the effect that detomidine has on the excretion of drugs administered at the same time resulting in a higher plasma concentration than that achieved when buprenorphine is given alone (Pakkanen et al., 2015). In order to investigate this hypothesis plasma samples would have needed to be taken for buprenorphine concentration determination. In addition local anaesthetic blocks were used as part of the analgesic protocol – if these were effective the requirements for buprenorphine would have been reduced. Sublingual use of buprenorphine has been reported in a five month old thoroughbred filly with a cervical vertebral fracture (Walker, 2007). A dose of 0.006 mg/kg bwt was given twice daily with onset of analgesia and sedation subjectively assessed to occur 45 minutes after administration into the interdental space. Mucosal absorption of buprenorphine following sublingual administration may provide a practically easy method of providing longer duration postoperative analgesia.

Butorphanol is the most commonly used opioid in equine practice (Wohlfender et al., 2015). In nociceptive studies of visceral and superficial pain 0.2 mg/kg bwt was suggested as the

optimal dose (Kalpravidh et al., 1984a). The duration of analgesia for visceral pain was 4 hours after 0.22 mg/kg bwt, compared to 1 hour of visceral analgesia after 0.66 mg/kg bwt morphine (Kalpravidh et al., 1984b). Despite this, no improvement in recovery quality or a reduction in inhalational requirement has been seen during anaesthesia (Bettschart-Wolfensberger et al., 2011, Dias et al., 2014). Postoperative CRI of butorphanol at 13 mg/kg/hr was associated with lower plasma cortisol concentrations, improved behaviour scores and less bodyweight loss (Sellon et al., 2004). This finding is consistent with the horses receiving butorphanol CRI postoperative experiencing less pain. It has been demonstrated to be an ineffective sole analgesic following castration (Love et al., 2009).

Methadone has a UK Marketing Authorisation for use in cats and dogs. A dose of 0.2 mg/kg bwt has been demonstrated to have an antinociceptive effect to mechanical, thermal and electrical stimulus when administered in combination with acepromazine or detomidine to horses, with the combination of methadone and detomidine having the greatest effect (Lopes et al., 2016). In a lipopolysaccharide induced synovitis model methadone was found to produce analgesia with less reduction in gastrointestinal sounds than morphine (Carregaro et al., 2014). If this finding is found to be consistent in clinical cases this may alleviate some of the concerns of postoperative ileus after morphine. Studies on the analgesic effect of methadone on animals experiencing clinical pain are currently limited.

Transdermal fentanyl patches have been used to treat horses with pain non-responsive to NSAID treatment, application of either one or two 10mg fentanyl patches to the antebrachium was found to reduce pain but not lameness scores. Uptake of drug is varies between sites of application; the thorax or groin results in greater systemic absorption with shorter lag time than the limb (Mills and Cross, 2007). The method used to prepare the area for transdermal drug administration has an effect on the systemic absorption as does variation in skin thickness between sites (Mills and Cross, 2006, Mills et al., 2004). The time taken to

reach analgesic serum concentrations varies from 1 to 14 hours (Thomasy et al., 2004, Maxwell et al., 2003), and in one study plasma concentrations of fentanyl failed to reach analgesic levels in 33% of horses (Orsini et al., 2006). Transdermal patches were found to be easy to apply and well tolerated in foals, but similar to adults systemic absorption was variable with no assessment of analgesic provision (Eberspacher et al., 2008). Based on the studies when placing a transdermal fentanyl patch the skin should be clipped and prepared with alcohol and chlorhexidine soloution (Mills and Cross, 2006). The most appropriate site to apply the patch is the thorax. Due to impracticalities of keeping the patch in position use of a limb is better suited for keeping the patch in contact with the skin. The variable lag time and systemic absorption means that the use of transdermal fentanyl patches requires close attention to the monitoring of pain scores, but may be useful for long lasting analgesia of outpatients postoperatively.

Lidocaine

Lidocaine is often used systemically for its prokinetic properties in horses with colic, its analgesic properties have also been shown in horses undergoing castration (Murrell et al., 2005), and its use is associated with a reduction in the use of inhalational agents (Schuhbeck et al., 2012). Its use in standing horses resulted in analgesia to a thermal stimulus but not to colorectal distension, suggesting a possible role in managing somatic pain (Robertson et al., 2005).

The potential for adverse effects should be considered when lidocaine is used systemically, neurological signs of toxicity include rapid blinking, anxiety, visual disturbance and ataxia and may be seen at doses of 30 µg/kg/min (Meyer et al., 2001). Horses that had a 1.5 mg/kg bwt loading bolus developed clinical signs earlier than those horses that did not, with cardiovascular signs of toxicity not apparent at doses causing neurological signs. The

systemic dose needed to produce toxic side effects may be reduced in compromised patients due to a slower hepatic clearance of the drug. General anaesthesia may make recognition of toxicity harder. A bolus of lidocaine before CRI is often used, but this may not be required as no inhalant sparing effect or difference in cardiopulmonary parameters and recovery scores was found between horses that did or did not receive a loading bolus whilst under isoflurane anaesthesia (Nannarone et al., 2015). Not giving a loading bolus may reduce the potential for reaching a toxic threshold.

Intraoperative administration of lidocaine may have a negative impact on quality of recovery from general anaesthesia (Schuhbeck et al., 2012, Valverde et al., 2005) so it is recommended that the lidocaine CRI should be stopped at least 30 minutes before transfer to the recovery box and also that additional sedation in recovery may be required (Valverde et al., 2005).

One study supports the therapeutic role of lidocaine in horses with ileus by reduction in reflux and shorter length of hospitalisation (Malone et al., 2006), however a more recent study found no effect of lidocaine administration on total reflux volume or duration, or on postoperative survival (Salem et al., 2016). Equivocal results on its use for analgesia and reduction of postoperative ileus mean that lidocaine should not be relied upon to provide post-operative analgesia and other analgesics should be administered concurrently.

Non-Steroidal Anti Inflammatory Drugs

NSAIDs remain the mainstay of analgesia in horses and, unless there is a contra-indication to their administration, should be included in the analgesic protocols of horses undergoing surgery . The variety of formulations and their long duration of action make them an attractive choice, with phenylbutazone and flunixin the most commonly used drugs (Wohlfender et al., 2015, Price et al., 2002). Clinical experience and familiarity probably form the basis of NSAID selection in clinical practice. Clinicians often express a preference

for the use of Phenylbutazone in horses with orthopaedic pain and Flunixin for horses with visceral pain, though this is not supported by the evidence (Johnson et al., 1993). Pre-emptive administration of NSAIDs may also help to reduce the likelihood of development of central sensitisation as has been shown with opioid and NSAID administration in other species (Lascelles et al., 1998, Lascelles et al., 1997) and timing their administration so that they are given before surgery means that they will be having an analgesic effect when the effects of anaesthesia are waning.

NSAIDs act by inhibition of cyclo-oxygenase (COX-1 and -2) enzymes, resulting in a reduction in the production of prostaglandins and thromboxane. COX-2 selectivity was thought to be preferential with COX-1 being a constitutive enzyme required for coagulation, protection of gastric mucosa and maintenance of renal blood flow. It is now known that COX-2 is also a constitutive enzyme in the eye, central nervous system and kidney, with COX-2 required for the healing of gastric ulcers. Potential adverse effects reported for NSAID use at therapeutic doses in the horse include gastric ulceration, renal dysfunction and right dorsal colitis (Andrews and McConnico, 2009).

Meloxicam is a COX-2 selective NSAID that is licenced for the treatment of acute and chronic musculoskeletal disorders and colic. Evidence also exists to suggest a beneficial effect on healing of the intestinal mucosa following ischaemic injury when meloxicam is used (Little et al., 2007). When compared to flunixin for provision of postoperative analgesia following surgery for strangulating small intestine, meloxicam showed no difference in analgesia based upon clinical evaluation, however when pain scores were compared horses that received flunixin had significantly lower scores (Naylor et al., 2014)..

Firocoxib is licenced for the treatment of pain associated with osteoarthritis, and vedaprofen for the treatment of postoperative pain. Firocoxib has shown to work as well as both

Phenylbutazone and Vedaprofen for treatment of osteoarthritis without treatment related side effects (Doucet et al., 2008, Koene et al., 2010).

The use of topical NSAID creams and gels is reported clinically, with a cream containing 1% diclofenac sodium available outside the UK. There is a lack of evidence to support the clinical use of these preparations.

Other Systemic Analgesics

The use of gabapentin is documented in case reports for the treatment of neuropathic pain unresponsive to other treatments (Davis et al., 2007), and management of severe hoof pain in combination with other systemic analgesics (Dutton et al., 2009). Tramadol co-administered with a low dose of ketamine was successfully used as part of an analgesic protocol in a horse with pain due to laminitis (Guedes et al., 2012). Tramadol 5mg/kg bwt orally every 12 hours for 1 week gave limited analgesia for three days only. The addition of a ketamine infusion at 0.6 mg/kg/hr, for 6 hours on the first three days of treatment, significantly increased the level and duration of analgesia. An experimental study reported a lack of anti-nociceptive effects against thermal, electrical or pinprick stimulation following administration of tramadol at 2 mg/kg bwt i.v. (Dhanjal et al., 2009, Seo et al., 2011) although the duration of antinociception following xylazine administration was extended by the concurrent use of tramadol (Seo et al., 2011) suggesting that it may play a useful role as part of a multimodal analgesic protocol. The use of paracetamol as an adjunct treatment for laminitis has also been described in a pony (West et al., 2011). Further research is needed before routine use of these drugs can be recommended although their use can be considered on an individual case basis.

Locoregional Techniques

Local Anaesthesia

The use of local anaesthetics for the diagnosis of lameness in horses is commonplace; the same techniques and drugs can also be used for the provision of effective perioperative analgesia. The versatility of this class of drug means that it can be used in multiple different ways, with a technique available for most situations. Local anaesthetics stop the transmission of the pain signal by binding to and blocking Na^+ channels when they are in the open or inactivated state, for this reason nerves of high firing frequency are most likely to be blocked. One limitation of the local anaesthetics is their reduced performance in infected tissues, this is due to the altered pH of the tissue affecting the fraction of unionised drug (Ueno et al., 2008). In this instance a nerve block at a site remote from the infected tissue may be of benefit.

The use of nerve blocks to facilitate dental and ophthalmic procedures in the standing and anaesthetised horse is well described. The inferior alveolar (mandibular) block will desensitise the mandible and lower dental arcade (Harding et al., 2012) and the maxillary block desensitises most structures of the maxilla including the rostral maxilla, paranasal sinuses and upper dental arcade (Bardell et al., 2010). Accidental blockade of the lingual nerve has been reported to occur with blockade of the mandibular nerve resulting in self trauma of the tongue (Caldwell and Easley, 2012). When performing nerve blocks of the horse's eye it should be remembered that the auriculopalpebral/palpebral nerve supplies only motor function and, although a block of this nerve will aid in examination of the eye, it does not desensitise any structures. Blockade of the frontal, lacrimal, zygomatic and infratrochlear nerves will desensitise the periorbital region. A retrobulbar block will facilitate enucleation, but may need to be accompanied by an auriculopalpebral block for immobilising the upper eyelid.

Infiltration of local anaesthetic into the testicle, cord and subcutaneously before castration in standing, sedated horses is routine; this technique is also useful in anaesthetised horses and

may reduce the incidence of movement as well as requirement for supplemental doses of anaesthetics (Portier et al., 2009). Subcutaneous infiltration of local anaesthetic is easy to perform before wound closure.

Increasingly, orthopaedic surgery is being performed in standing, sedated horses and nerve blocks can improve surgical conditions and reduce the requirements for additional chemical restraint. In standing, sedated horses distal limb blocks should be performed before arthroscopy or fracture repair, with specific nerve blocks often being used alongside a ring block (Payne and Compston, 2012). Intravenous regional techniques for delivery of antimicrobials is commonly implemented in equine practice and the same technique can be used to desensitise the distal limbs. Desensitization of the limb being operated on with local anaesthesia can also be considered in horses having the procedures done under general anaesthesia. Careful thought should be given to the individual case as ataxia and effects on control of the limb are potential hazards during recovery from anaesthesia.

Intraarticular injection following arthroscopic procedures can contribute to postoperative analgesia. Morphine, local anaesthetics and the alpha-2 adrenoceptor agonists all provide analgesia for inflamed joints (van Loon et al., 2010). Caution must be used as systemic uptake of the drugs still occurs and systemic side effects can still be seen (Di Salvo et al., 2014). Concern over chondrotoxicity of the local anaesthetics has been a topic of discussion in recent years. In an in vitro cell culture preparation of equine chondrocytes mepivacaine was the least chondrotoxic, with bupivacaine showing the most chondrotoxicity to equine cartilage (Park et al., 2011). However, in vivo effects do not always mimic the changes seen in laboratory cell culture preparations and the method of delivery of the local anaesthetic probably has a significant impact on the effects of local anaesthetics on chondrocytes since in people continuous infusion of local anaesthetic into the joint has a more deleterious effect than would be expected from a drug effect alone (Dragoo et al., 2008). A single injection of a

low concentration of local anaesthetic would appear to be safe, whereas the effects of a continuous infusions require further investigation (Webb and Ghosh, 2009).

When morphine (0.05 mg/kg) is given intraarticularly, to horses with lipopolysaccharide induced synovitis, it is detectable within the synovial fluid for 24 hours and results in less swelling and lameness than the same dose of morphine given IV (Lindegaard et al., 2010a, Lindegaard et al., 2010b, Lindegaard et al., 2010c). The reduced swelling of the joint when morphine was given intraarticularly supports morphine having a peripheral anti-inflammatory effect as well as a central mechanism of action. Despite a reduction in lameness there was no difference in pain score between the two routes of administration (Lindegaard et al., 2010c).

Paravertebral thoracolumbar anaesthesia in horses having standing laparoscopic procedures produces good to excellent anaesthesia in 80% of cases (Moon and Suter, 1993).

Epidural and Subarachnoid Anaesthesia and Analgesia

Epidural anaesthesia was first described in the horse almost 100 years ago (Pape and Pitzschk, 1925). Use of both a single injection and repeated dosing via an epidural catheter are options for both intra-operative and post-operative analgesia. Local anaesthetics, opioids and alpha-2 adrenoceptor agonists can all be administered via the epidural space, though it must be remembered that systemic uptake of the drugs will occur and side effects of may become apparent for example, sedation and ataxia Epidural injections are most commonly performed via the first intercoccygeal space, with location of the space most practically identified by repeatedly raising and lowering the tail.. Subarachnoid injection, where the drug is injected into the cerebrospinal fluid rather than the epidural space, can be performed at the lumbar-sacral (L7-S1) space, though this technique is more challenging and often resented by the horses (Natalini and Driessen, 2007) which limits its use clinically.

Opioids, most commonly morphine, are used for epidural analgesia. Opioid receptors are found extensively in the dorsal horn of the spinal cord, and opioid agonists can provide effective and long-lasting pain relief (Valverde et al., 1990, Cousins and Mather, 1984). Analgesia can be achieved as far cranially as the thoracic dermatomes after a single epidural injection of morphine diluted to a volume of 20mL (Natalini and Robinson, 2000). Another potential benefit is that morphine administered into the epidural space has also been found to inhibit the development of hyperalgesia in an experimental model of synovitis (van Loon et al., 2012).

Concern over side effects is similar when administering opioids in the epidural space as when they are given systemically although the dose administered epidurally is usually lower that that given systemically which should reduce the risk or intensity of side effects. In healthy horses morphine reduced gastrointestinal transit times in healthy horses but not when used for provision of analgesia for laparoscopic castration (Sano et al., 2011, Martin-Flores et al., 2014) indicating differences in effects between healthy and painful horses.

Both methadone and buprenorphine also provide effective analgesia when given epidurally. Methadone provides effective analgesia but with a shorter duration than that reported for morphine (Olbrich and Mosing, 2003). In horses undergoing bilateral stifle arthroscopy epidural buprenorphine plus detomidine produced analgesia of similar intensity and duration to that provided by morphine and detomidine (Fischer et al., 2009).

Combining a local anaesthetic with an opioid extends the duration of analgesia compared to the use of an opioid alone (Hendrix et al., 1996). However, care should be taken with the volume of local anaesthetic used as cranial spread can impair the function of the pelvic limbs and cause ataxia or even paralysis. If an epidural including a local anaesthetic is to be administered consider restraining the horse in stocks and ensure that everyone working with

the horse is aware that ataxia is a potential risk. The total volume used will depend on the size and conformation of the horse and the drug or combination of drugs used. Less than 10mL total volume should be used in adult horses if a combination including a local anaesthetic is used, as cranial spread of volumes greater than this may cause hindlimb paralysis and recumbency of the patient (Natalini and Driessen, 2007).

Alpha-2 adrenoceptor agonists administered epidurally can increase both the sensory and motor blockade compared to an opioid or local anaesthetic used alone. Speed of onset is quicker and an extended duration of action is also seen (Grubb et al., 1992). Doses of other drugs given at the same time should be reduced. Systemic uptake of the drug also occurs and signs of sedation, ataxia and cardiovascular changes such as bradycardia and atrioventricular block may become apparent.

Adjunctive Therapies

When devising a perioperative analgesia plan the use of non-drug therapy should also be considered. Good nursing care is imperative and in addition the use of cold packs on inflamed tissues and physiotherapy when appropriate will also help. Although acupuncture is frequently employed by equine veterinarians in the treatment of chronic pain (Bergenstrahle and Nielsen, 2016) its efficacy for treatment of acute pain and in the perioperative period is unknown. Its use for the treatment of colic pain has been shown to be less effective than butorphanol in one method (Skarda and Muir, 2003) and ineffective in another (Merritt et al., 2002).

Conclusion

The ability to recognise pain behaviours in horses is an essential skill of the equine veterinarian. The publication of clinically useful pain scales for this species will further aid in the recognition of pain in the perioperative period. Careful consideration should be given to

436 the mechanism of the pain stimulus when planning a surgery and an analgesic plan. Table 2
437 suggests when each therapy should be used. The use of multimodal analgesia utilising drugs
438 from different classes and given both systemically and locoregionally will improve outcomes
439 and the welfare of patients.

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